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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	J.C. Kennedy et al
Serial No.:	07/783,750
Filed:	October 28, 1991
For:	METHOD OF DETECTION AND TREATMENT OF MALIGNANT AND NON-MALIGNANT LESIONS BY PHOTOCHEMOTHERAPY
Our File:	Q1352

September 11, 1992

Hon Commissioner of Patents
and Trademarks
Washington, D.C.
20231

Dear Sir:

This is in response to the Official Action of 9 July 1992.

The Examiner's objection to the specification and rejection of claims 4 and 5 under 35USC112 first and second paragraphs are respectfully traversed. It is respectfully submitted that applicant has provided an enabling disclosure and that the Examiner's objection that no example of diagnostic use has been given is totally without foundation. The Examiner's attention is directed to Example 5 on page 15 which is clearly directed to diagnostic use. It is pointed out that Example 5 teaches a dosage range of 100 to 500 mg amino levulinic acid (ALA) per kg of body weight which is shown to be "effective". Dosage rates for topical application for therapeutic use and described in Examples 1-4 and range from 35-100 mg ALA per lesion (or considerably less than the dosage used for diagnostic purposes.)

It is submitted that while page 11 of the disclosure teaches that very large doses (i.e.

in excess of 1000-1200 mg/kg) of ALA are associated with transient decrease in motor nerve conduction velocity this is not to say that ALA which is a naturally occurring substance present in the human body is toxic. As used herein the term "transient" is an art term and those skilled in the art know that such a transient effect has dissipated in 8-10 days from administration. This is hardly a "toxic" effect but more akin to hitting ones humeral bone (funny bone) and causing a transient numbness of the fingers thereby - also an effect of motor nerve conduction velocity. Applicant has clearly described a range of ALA for diagnostic use of between 100 and 500 mg per kg of body weight as being effective and it is therefore submitted that an enabling disclosure which fully supports "an effective amount "in claim 4 has been provided. Reconsideration and withdrawal of this objection is respectfully requested.

The rejection of claims 4 and 5 as obvious under 35USC103 over Blumberg in view of Gordon and Fukuda is respectfully traversed. It is submitted that the Examiner has taken Blumberg entirely out of context and that Blumberg in no way suggest applicants method for detecting malignant and non-malignant tissue abnormalities, such as cancer. Blumberg makes use of the old and well known fact that the concentration of endogenous zinc protoporphyrins and other free base protoporhyrins increases in the presence of lead ions in whole blood. Thus, to determine the extent of lead contamination in whole blood it is merely necessary to measure the increase in fluorescence of the endogenous protoporphyrins. It is to be noted that zinc protoporphyrin is excited at 425 nm and emits at 595 nm and that interference filters are used to separate out all excess protoporphyrin emissions. Blumberg neither uses nor suggests how ALA might be used to determine lead poisoning. Blumberg merely states that -aminolevulinic acid is a candidate metabolite.

Presumably he infers that assay of endogenous ALA would be a measure of lead contamination but it will be appreciated also that ALA per se is not a fluorogenic agent and the assay would not be fluorogenic in nature. In contrast applicants do not measure fluorescence of endogenous zinc protoporphyrins at all. Applicants rely on exogenous ALA to stimulate in vivo production of metal free or iron protoporphyrins which accumulate preferentially in abnormal tissues and which are excited at 410 nm and which emit fluorescence at 650-700 nm - ranges which are excluded by Blumberg.

It is further submitted that Gordon and Fukuda either alone or in combination fail to remedy the deficiencies of the primary reference to Blumberg. Gordon teaches the intravenous injection of preformed metalloporphyrin particles suspended in a liquid into a patient so that the metalloporphyrins selectively accumulate in cancer cells. The metalloporphryins are then subjected to a high frequency alternating electromagnetic field so as to preferentially heat the metalloporphryins and their host cells, and thus kill the cancer cells. In contrast applicant does not employ preformed protoporphyrins, and does not employ electromagnetic fields to heat the cancer cells. A solution of ALA is administered so as to generate protoporphyrin in situ in the cancer cell which is subjected to light in the visible spectrum. Fukuda is equally remote in that he teaches the use of a series of preformed porphyrins which can be administered to a cancer-bearing living body and which accumulate preferentially in the cancerous tissue and fluoresce under light irradiation. Here again it is emphasized that the porphyrins - not even protoporphyrins are entirely different chemically and are administered in a preformed state. There is no suggestion for administering a precursor and generating a selected protoporphyrin in vivo as in the present invention.